Review

Allergies to Allergens from Cats and Dogs: A Review and Update on Sources, Pathogenesis, and Strategies

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Review

Allergies to Allergens from Cats and Dogs: A Review and Update on Sources, Pathogenesis, and Strategies

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Abstract: Inhalation allergies caused by cats and dogs can lead to a range of discomforting symptoms, such as rhinitis and asthma, in humans. Given the increasing popularity and care provided to these companion animals, the allergens they produce pose a growing threat to the health of susceptible patients. Allergens from cats and dogs have emerged as significant risk factors for triggering asthma and allergic rhinitis worldwide; however, there remains a lack of systematic measures aimed at assisting individuals in recognizing and preventing allergies caused by these animals. This review provides comprhensive insights into the classification of cat and dog allerges, alongwith their pathogenic mechanisms. The study also discusses implementation strategies for prevention and control measures, including physical methods, gene editing technology, immunological approaches, as well as potential strategies for enhancing allergen immunotherapy combined with immunoinformatics. Finally, it presents future prospects for the prevention and treatment of human allergies caused by cats and dogs. This review will improve knowledge regarding allergies to cats and dogs, while identifying potential targets for the development of next-generation treatments

Keywords: allergy; pet allergen; epitope; IgY antibody; immunotherapy

1. Introduction

Allergic reactions, also known as type I hypersensitivity, occur when the body's pre-existing immunity system is exposed to the same allergen again, resulting in an excessive immune response mediated by immunoglobulin E (IgE). Common clinical symptoms include urticaria, eczema, asthma, rhinitis, vomiting, diarrhea, and potentially life-threatening anaphylactic shock [1]. It is a prevalent global condition with ubiquitous allergens that trigger these reactions in daily life, such as pollen, food, dust mites, bacteria, animal dander, and insect bites [2].

Among these allergens, cat and dog dander are considered significant factors in the development of allergic asthma and rhinitis, with their prevalence increasing over time [3]. Approximately 10-20% of surveyed individuals exhibit sensitivity to cat dander, while 12-18% are sensitive to dog dander [4,5]. In a study investigating allergies conducted in China, it was found that both cats and dogs play a crucial role in triggering allergies by testing levels of allergen-specific antibodies in patients [6]. The growing population of cats and dogs in China implies an increasing threat from the presence of dog and cat allergens present in the air. Furthermore, it has been observed that allergens from cats and dogs are significant contributors to allergic reactions worldwide (Table 1). Notably, the prevalence of sensitization to cats and dogs can exceed one-fifth in developed nations [19]. Individuals who keep pets at home inadvertently transport allergens to their workplace, resulting in a 57.6% higher median concentration of allergen Fel d 1 among offices owned by cat owners compared to non-cat owners; similarly, there is a 77.14% higher median concentration of Can

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f 1 among offices owned by dog owners compared to non-dog owners [20]. Even individuals lacking prior experiences in pet ownership can identify the presence of cat and dog allergens within their households if they reside in communities with high rates of pet keeping [21]. Additionally, it has been observed that specific cat allergens persist in indoor air for a duration of 6-9 months even after pets have been removed [22]. These findings undoubtedly contribute to an increased risk of allergic diseases caused by pets, imposing significant health and economic burdens on the general public.

Currently, there is a lack of convenient and effective methods for the treatment of human allergies to cats and dogs. One predominant approach involves alleviating allergic symptoms through the administration of antihistamines, corticosteroids, or decongestants [23]. Another method is allergen immunotherapy, which needs gradually increasing exposure to allergens to facilitate adaptation without eliciting excessive reactions. However, these treatments have prolonged durations and desensitization vaccines are susceptible to adverse reactions [24].

In this study, we conducted a comprehensive literature survey on allergens from cats and dogs, providing detailed insights into their classification and pathogenic mechanism. Moreover, we summarized recent advancements in strategies for the prevention and treatment of allergic diseases, followed by methods to enhance immunotherapy.

2. Sources of Allergens

The World Health Organization (WHO) has registered eight allergens each for both cats and dogs (Table 2). Among cat allergens, Fel d 1, Fel d 7, and Fel d 4 exhibit the highest frequencies of IgE recognition and the ability to activate basophilic granulocytes. The median allergen concentration required to reach activation plateau in a basophilic leukemia cell line, which expresses human high affinity IgE receptor (FcεRI), is at levels of 0.1, 1, and 1 ng/mL, respectively, nearly 100-fold higher than that of Fel d 6 and Fel d 8 [30]. Among dog allergens, Can f 1 accounts for approximately 70% of allergies while Can f 5 and Can f 6 account for over 30% [43]. It should also be noted that individuals may have simultaneous sensitivity to multiple allergens due to cross-reactivity between cat and dog allergens caused by sequence conservation with a cross-sensitivity rate of 48% [44,45].

2.1. Lipocalin

The allergens Fel d 4, Fel d 7, Can f 1, Can f 2, Can f 4, and Can f 6 from cats and dogs belong to the lipocalin family and commonly induce respiratory allergies. Lipocalins exhibit a diverse range of functions including retinol transportation, pheromone transport, prostaglandin synthesis, immune regulation, and cellular synthesis [46]. They consist of approximately 150-250 amino acids each with low conservation and homology. Dog Can f 1 shares only 25% similarity with human lipid transport protein 1 (LCN1) [47]. However, they also possess one to three structurally conserved regions (SCR1-SCR3) and exhibit a high degree of similarity in the tertiary structure, comprising eight reverse parallel β-strands, forming a central β-barrel structure closely associated with α-helix. Within this barrel-like structure, hydrophobic ligand binding sites are present, enabling them to carry various lipophilic small molecules and perform diverse physiological functions [29,48]. Furthermore, an additional functional characteristic of lipocalins is their ability to act as specific ligands that bind to cell surface receptors. Cat Fel d 4 can serve as ligands activating the vomeronasal organ of mice, a special chemosensory epithelium responsible for eliciting defense responses against predators [49].

The allergen database contains a total of 19 lipid transport protein allergens from 10 mammalian species. However, there is still limited understanding regarding the underlying mechanisms behind their ability to induce allergic reactions. Due to the tendency of lipid carrier proteins to form oligomers such as o dimers (Can f 4) or tetramers (Can f 2), these allergenic oligomers may impact the cross-linking of FcεR I receptors and subsequently influence mast cell activation [50]. The allergenicity of lipocalins might be associated with their capacity to bind specific cell surface receptors. Pierre et al.; through gene silencing, has demonstrated suppression in mannose receptor expression on dendritic cells (DCs) from human peripheral blood monocytes, while also inhibiting recognition and uptake of Can f 1 protein [51]. Additionally, other studies have shown that cell

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surface heparan sulfate proteoglycans (HSPG) function as endocytic receptors involved heterologous Fel d 4 uptakes [52].

Owing to their structural similarity, lipocalins produced by different species may possess identical antigenic determinants that can bind to the same antibodies, thereby exhibiting immune cross-reactivity between Can f 2, Can f 6, and Fel d 4. Regrettably, there are currently insufficient evidences regarding the correlation between the allergenicity of the lipid transport protein family and its structure and function.

2.2. Immunoglobulin

Immunoglobulins are dimeric proteins consisting of two heavy and light chains, secreted by plasma cells derived from B-cells. The immunoglobulins expressed on the surface of B-cells are commonly referred to as B-cell receptors, while the soluble form of immunoglobulins is known as antibodies. Based on their structure, distribution, composition, and function, immunoglobulins include immunoglobulin G (IgG), immunoglobulin A (IgA), immunoglobulin M (IgM), immunoglobulin D (IgD), and IgE. Cat Fel d 5 and Fel d 6 correspond to IgA and IgM, respectively. The glycan portion of cat's IgA serves as the primary antigen-binding site for human-produced IgE [3,54].

2.3. Serum Albumin

Serum albumin is widely distributed throughout various mammalian organisms and belongs to a class of multifunctional proteins that exhibit high conservation in both sequence and structure. Its primary functions include osmotic pressure regulation, small molecule transportation, and pH buffering [55]. Additionally, serum albumin has been identified as an allergen in human. Cat Fel d 2 and dog Can f 3 are members of the serum albumin family; they not only exhibit immunological cross-reactivity with each other but also with serum albumin from other mammals such as horses. This cross-reactivity can be attributed to the extensive preservation of antigenic epitopes resulting from sequence and structural similarity [56].

2.4. Cystatin

The proteins cat Fel d 3 and dog Can f 8 are membranes of the cystatin family, a class of natural reversible inhibitors that tightly bind to cysteine proteases. Given the widespread presence of cysteine proteases in organisms, which perform various physiological functions, cystains play a crucial role in regulating these enzymes [57].

Additionally, secretoglobin Fel d 1, a representative allergen in cats, is the primary causative agent of human allergies. It exists as a tetrameric glycoprotein composed of two non-covalently linked heterodimers, each with an approximate molecular weight of 18 kDa [58]. Chain 1 of Fel d 1 shares approximately 30% sequence homology with other uteroglobin proteins, while chain 2 exhibits minimal homology [59]. Previous studies have demonstrated that males secret higher levels of Fel d 1 than females [60]. However, the precise mechanisms underlying its allergenicity and physiological functions remain unclear. It has been shown that Fel d 1 can significantly enhance immune signal transduction through Toll-like receptors (TLR4 and TLR2) on immune cell surfaces and can bind to lipopolysaccharide (LPS) to amplify TLR signaling. Furthermore, it has been found that the cell surface mannose receptor plays an essential role in DCs' uptake of Fel d 1 by binding allergens via its cysteine domain to sulfated acidic polysaccharide structures on allergens [61].

However, upon comparing natural Fel d 1 with recombinant expressed Fel d 1 proteins exhibiting different levels of glycosylation in baculovirus and Pichia pastoris, a significant increase in tumor necrosis factor α (TNF-α) expression was observed in mouse bone marrow-derived macrophages when combined with LPS. Importantly, this enhancement was not elicited in TLR4-deficient mice. These findings suggest that the mechanism underlying Fel d 1's activity may be related to ligand-protein interactions and the TLR4/TLR2-mediated immune pathway, which operates independently of the mannose receptor on DCs' surfaces. Given that Fel d 1 is primarily

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located in glandular regions such as the cat's perianal area, it could potentially function as a feline pheromone or serve as a carrier for pheromone transmission due to its ability to bind small molecule ligands within its hydrophobic cavity [62].

The kallikrein-like prostatic allergen Can f 5, which is regulated by male hormones, is exclusively detectable only in male dogs and has been identified as the sole allergen in approximately one-third of individuals with dog allergies [63]. There have been reported cases of individuals who previously had no adverse reactions to semen exposure but developed allergies to semen in public places [64]. with a notable presence of specific IgE against Can f 5. Furthermore, Can f 5 shares around 55-60% structural homology with human prostate-specific antigen and exhibits immunological cross-reactivity between them [65].

3. Pathogenic Mechanisms of Allergens

Cat and dog allergens are typically small molecular proteins synthesized in various glands or the liver. Once secreted, they primarily localize in the pet's skin, hair, and body fluids such as saliva, milk, urine, and sweat. During shedding of hair and dander by animals, these allergens can adhere to dust particles and disperse throughout the environment. Upon inhalation of these allergens, antigen-presenting cells (APCs) and predominantly DCs can capture them and present them to T cell receptors (TCRs) through major histocompatibility complex (MHC) molecules on naive T cells' surface. This process promotes their differentiation into helper 2 cells (Th2). Subsequently, Th2 cells secrete cytokines including interleukin 4 (IL-4), interleukin 5 (IL-5), interleukin 13 (IL-13), interleukin 9 (IL-9), and interleukin 10 (IL-10) that stimulate B lymphocytes to produce specific IgE antibodies targeting allergens while inducing their proliferation as well as differentiation into memory B cells or plasma cells. Plasma cells in the bone marrow can continuously produce IgE which enters the body fluid circulation and binds to FcεRI on mast cells and basophils causing a temporarily asymptomatic sensitization state. Upon re-exposure to allergens, cross-linking of specific IgE bound to mast cells or basophils triggers a signaling cascade leading to mast cell activation and degranulation (Figure 1). This results in the release of pre-stored and newly synthesized mediators such as histamine, arachidonic acid, prostaglandins, causing urticaria, eczema, asthma, rhinitis, vomiting, and diarrhea [66–71].

Few studies have revealed that micronutrients, particularly iron, play a crucial role in regulating the immune system. Iron indirectly influences the proliferation, differentiation, and function of immune cells such as macrophages, mast cells, T cells, and B cells through various mechanisms involving iron regulatory factors and transporters [72]. Insufficient iron levels can activate antigen-presenting cells, promote Th2 cell generation, and facilitate class switching in B cells. Therefore, it has been hypothesized that inadequate iron content within immune cells may contribute to allergic reactions [73–75].

4. Strategies for Preventing and Treating Allergies

4.1. Physical Methods

The removal of pets from the household has been demonstrated as an effective approach in reducing adverse reactions among patients with pet allergies [76]. By comparing the allergen content in 50 households with cats and 50 without, it was discovered that the disparity in allergen levels in carpets and soft furnishings reached levels as high as 200-300 times [77]. After removing cats from 15 households, there was a significant decrease in Fel d 1 level in the air by several hundred times over a period ranging from 9 to 43 weeks. Remarkably, even one group achieved allergen levels comparable to those observed in cat-free households [76]. Therefore, avoiding direct contact with pets remains the most straightforward and efficacious method for preventing human allergies.

Utilizing tap water or pet-specific bathing products for approximately 60 seconds can effectively reduce airborne allergen by over 40% [78]. Similarly, washing dogs at least twice a week can also lead to a significant reduction in airborne allergen concentration by at least 40% within a short period of time [79]. Due to the favorable solubility properties of most pet allergens, regular laundering of

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textiles using washing machines and appropriate detergents can eliminate over 95% of allergens [80]. Furthermore, air filters play an instrumental role in significantly reducing pet allergen levels in indoor environments [81,82]. By incorporating air filters, it is possible to achieve an impressive reduction rate of 84% for dog allergens within enclosed spaces (Figure 2) [83]. In another study, the proportion of patients with cat allergies who developed early asthma in a room containing cat allergens under placebo conditions was three times higher than those exposed to a room with cat allergens and an operational air purifier [84]. However, when Gore et al. tested the effectiveness of different brands of high-efficiency new vacuum cleaners and old control vacuum cleaners in removing allergens; they found that exposure to cat allergens increased by three to five times [85]. Although air purifiers can significantly reduce inhalable dust levels during household activities, there is no statistically significant reduction in pet allergen concentration [86]. Air purifiers can effectively decrease over 90% of indoor pet allergens and alleviate allergic symptoms in a mouse model. Furthermore, the photoelectrochemical oxidative (PECO) Molekule filtration device (PFD) demonstrates a significant reduction in eosinophil recruitment associated with allergies compared to the HEPA-assisted air filtration device (HFD). Further detailed experimental investigations are necessary to determine the efficacy of air filters in controlling pet allergen concentrations in different environments, using various brands of air filters, and considering varying numbers of pets present [87].

4.2. Gene Editing

To effectively remove pet allergens, individuals are also exploring alternative long-term methods for reducing cat allergens. Gene-editing technology has been used to specifically target the genes responsible for producing allergen proteins at the genetic level, upstream of protein expression (Figure 2). The objective is to disable these genes and selectively breed cat breeds with reduced allergenicity [88]. By utilizing the CRISPR-Cas9 system and cytoplasm injection clone technology, Gene-edited cats have been successfully generated with lower levels of Fel d 1 expression [89]. While this approach offers a permanent solution for eradicating pet allergens, there remains limited understanding regarding the precise function of Fel d 1, which raises uncertainty about potential adverse effects on both individuals and their offspring resulting from knocking out a single gene. Furthermore, considering that there are at least eight types of cat allergens known to cause human allergies, additional uncertainty and risk inevitably arise.

4.3. Immunological Strategies

4.3.1. Allergen Specific Immunotherapy

Allergen-specific immunotherapy (ASIT) is an effective method of desensitization for patients with IgE-related allergies (Figure 2). Continuous administration through subcutaneous immunotherapy (SCIT), sublingual immunotherapy (SLIT), and intralymphatic immunotherapy (ILIT) induces immune tolerance, thereby preventing the activation of an immune response against specific antigens [90,91]. Potential mechanisms of AIT include a reduction in allergen-specific Th2 cells, activation of regulatory T and B cells, and production of "blocking" antibodies IgG and IgA [92]. In a three-year clinical trial involving 32 adults and children, cat and dog dander extracts were used for allergen-specific immunotherapy. The study observed a decrease in IgE levels, an increase IgG levels, and superior efficacy of cat immunotherapy compared to dog immunotherapy [93]. Unfortunately, 41% of patients with cat allergies who received subcutaneous injection of cat allergens experienced severe systemic reactions [94]. Therefore, further research is needed on antigen preparations that possess high immunogenicity while ensuring substantial quality and minimal toxicity.

4.3.2. Monoclonal Antibodies

Allergies are frequently triggered by the binding of allergens to IgE. A therapeutic approach involves identifying anti-IgE antibodies that can neutralize IgE and prevent its interaction with

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allergens. Akiko et al. have developed monoclonal antibodies known as CRE-DR against dog IgE, which have been validated through enzyme-linked immunosorbent assay (ELISA) for their specific reactivity to human IgE, indicating the potential of these monoclonal antibodies in treating allergies [95]. Omalizumab is a humanized monoclonal antibodies that selectively bind to circulating IgE, inhibiting the activation of inflammatory cells and the release of inflammatory mediators [96]. It has successfully completed clinical trials for various types of allergic asthma and is commercially available in several countries. In a clinical study evaluating omalizumab for cat allergen-induced allergies, the group receiving omalizumab demonstrated a significant reduction in acute asthma, achieving an efficacy rate of 62.9% [97]. However, administration of omazumab may result in adverse reactions such as headaches and pharyngitis [98]. Currently, there is a lack of further clinical trials investigating the effectiveness of anti-IgE antibodies in alleviating allergies to cats and dogs. Therefore, future research should focus on exploring more effective and safer anti-IgE antibodies, as well as combination prevention and treatment strategies.

The synthesized human IgG4 antibodies, REGN1908 and REGN1909, exhibit synergistical and competitive binding to allergens in a non-competitive manner, effectively impeding the interaction between allergens and IgE. This inhibition leads to the suppression of inflammatory mediator releases induced by allergens from eosinophils and mast cells. *In vitro* experiments have shown that both antibodies exhibit a half-maximal inhibitory concentration (IC_{50}) value of 0.45 nM, resulting in an 83% inhibition rate against IgE binding. Subsequent successful clinical trials conducted on mice and humans have demonstrated alleviation of allergic symptoms [99].

4.3.3. Immunoglobulin Y

Immunoglobulin Y (IgY) is a highly homologous polyclonal antibody in poultry, which specifically binds to corresponding antigens for antigen inactivation and play a crucial role in passive immunity. Following immunizing poultry with specific antigens, the resulting antibodies are transported through the bloodstream to the ovaries, where they gradually accumulate within egg cells and ultimately store in the yolk. Each egg can yield approximately 50-100 mg of IgY, while an individual chicken can produce over 20 g of IgY per year. The advantages of IgY include a well-established preparation process, high production yield, short cycle time, and adherence to animal welfare principles [100].

Due to the distant genetic relationship between species, IgY exhibits inherent high affinity for mammalian proteins [101]. Satyaraj et al. used specific chicken IgY targeting Fel d 1 to effectively inhibit the binding of Fel d 1 to IgE. In a feeding experiment conducted on cats, Fel d 1 levels in saliva was reduced by at least 20% when cats were fed with IgY antibodies [102]. Another study evaluated the safety of administering three different doses of anti-Fel 1 IgY antibodies to 27 kittens over a period of 84 d. The results showed that their weekly weight and physical condition scores remained within healthy ranges, and no abnormalities were observed during veterinary examinations and blood biochemistry analyses [103]. Undoubtedly, using specific IgY antibodies for neutralizing allergens produced by cats represents an economical, environmentally friendly, and safe approach; however, further cat feeding experiments and clinical evidence are still required for validation.

Additionally, β-lactoglobulin (BLG) is a well-known protein found in bovine milk whey. It binds with immune cells and carries iron, activating the aryl hydrocarbon receptor (AHR) pathway for immune regulation to enhance resilience and tolerance among these cellular components [75]. Bergmann et al. developed lozenges containing holoBLG-based micronutrients as supplements to prevent allergies to cats. Following a three-month treatment course with holoBLG, 35 patients exhibited increased tolerance to allergen concentrations during nasal provocation tests compared to pre-treatment levels; 20 patients experienced no allergic late-phase reactions [104]. These findings highlight the potential efficacy of targeted micronutrients delivered through holoBLG lozenges in preventing cat allergies, as well as other allergens [105].

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5. Strategies for Enhancing Allergen Immunotherapy

5.1. Vaccine Adjuvants and Modifications

The combination of different adjuvants with allergens can enhance the stability and immunogenicity of vaccines. Utilizing non-reactive immunological adjuvants in conjunction with antigens effectively stimulates relevant immune cells, thereby augmenting the immune response to the antigen [106]. Commonly employed adjuvants such as aluminum hydroxide, alum, and Freund's adjuvant have demonstrated notable success in generating immunity against viral and bacterial infections; however, further improvements are still required to enhance the protective antibody response. Andersson et al. utilized carbohydrate-based particles (CBP) covalently coupled with recombinant cat allergens, resulting in a significant increase (three to four times) in IL-8 release and TNF-α production by human monocyte-derived DCs [107]. Tasaniyananda et al. successfully employed liposomes as an immune adjuvant for specific immunotherapy in a murine model of feline allergy [108]. Similarly, Leonard et al. effectively treated the Fel d 1 allergic mouse model by using CpG oligodeoxynucleotides as an adjuvant [109]. Although the growing development of novel adjuvants, there is still a lack of comprehensive experimental evaluations regarding their combination with pet allergens. In recent clinical trials, Corren et al. used tezepelumab, a human monoclonal antibody targeting thymic stromal lymphopoietin (TSLP), as an adjuvant for ASIT in patients with cat allergy. Tezepelumab demonstrated its ability to reduce serum concentrations of IL-5 and IL-13, as well as total IgE levels in asthma patients while improving lung function and alleviating symptoms. Notably surpassing sole administration of SCIT, the incorporation of tezepelumab exhibited remarkable efficacy in reducing nasal reactions induced by allergens, with sustained effects even after one year [110].

Adjuvants not only effectively enhance the efficacy of ASIT, but also reduce production costs by decreasing the concentration and frequency of antigen administration. Different adjuvants exhibit distinct auxiliary effects on various antigens [111]. Currently, some novel adjuvants such as liposomes, oil-in-water emulsions, and TLR agonists have shown positive effects in ASIT. However, there is limited evaluations regarding the combined effects of adjuvants with diverse cat and dog allergens.

The safety of immune preparations can be enhanced by chemically modifying allergens to disrupt their IgE binding sites while preserving immunogenicity [112]. González et al. polymerized the natural extract of cat dander using glutaraldehyde, resulting in safer immune preparations that still maintain efficacy [113]. Calzada et al. modified Can f 1 and Can f 5 using glutaraldehyde and found that the polymer exhibited low IgE binding while effectively activating basophils in dog allergic patients [114]. However, it is yet to be proven whether common chemicals like formaldehyde, glutaraldehyde, and tyrosine are safe and effective for modifying pet allergens [115].

5.2. Recombinant Allergens

Extracting and purifying allergens from pets is undoubtedly an inefficient and time-consuming process, prompting scientists to focus on heterologous recombinant expression systems. Schmitz et al. successfully conjugated Fel d 1 with bacteriophage Qbeta-derived virus-like particles (Qbeta-Fel d 1), resulting in the fusion protein Qβ-Fel d 1. However, this highly immunogenic protein does not elicit basophils degranulation in humans with cat allergies or induce allergic reactions in mouse models [116]. Subsequently, Katarzyna et al. expressed a fusion protein in Escherichia coli by combining the PreS domain derived from hepatitis B virus with two non-allergenic peptides of Fel d 1. In mouse and rabbit immunization experiments, this fusion protein exhibited similar properties to Qbeta-Fel d 1 as it not only induced Fel d 1-specific IgG antibodies, but also inhibited the binding of IgE from allergic patients to the allergen [117]. Ogrina et al.; on the other hand, fused Fel d 1 with virus-like particles obtained from eggplant mosaic virus (EMV) and achieved high titers of Fel d 1-specific antibodies in mice [118]. By genetically fusing allergens with carriers that enhance stability and immunogenicity, fusion proteins exhibit higher immunogenicity while simultaneously reducing

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IgE reactivity. These fusion proteins can be efficiently produced through large-scale fermentation processes, thereby offering potential avenues for the development of AIT vaccines.

5.3. Epitopes

With more in-depth research on the structure and sensitization mechanism of allergens, scientists are increasingly focusing on the antigenic determinants (epitopes) of these proteins. Epitopes refer to specific regions on the surface of antigens that possess a distinct structure and immunological activity, capable of stimulating antibody production or sensitizing lymphocytes. These antibodies or lymphocytes recognize epitopes, which typically consist of less than 20 amino acid residues. Based on their continuity or discontinuity within the three-dimensional (3D) protein structure, epitopes can be classified as either linear or conformational [119].

Compared to intact allergens, artificially synthesized fusion epitopes not only encompass dominant protein epitopes, but also include hidden epitopes located within the antigenic molecules [120]. Norman et al. conducted a single-blind subcutaneous injection treatment on 95 cat-sensitive patients over a four-week period using two synthesized peptides, each containing 27 amino acids and based on the T cell epitopes of Fel d 1 (ALLERVAX CAT). The efficacy of the treatment was evaluated by assessing nasal and pulmonary symptoms in patients exposed to rooms occupied by live cats before and after the intervention. Following the four-week treatment, both the middle and high dose groups demonstrated significantly improved tolerance to cats compared to the control and low dose groups [121]. Worm et al. developed a Cat Peptide Antigen Desensitization (Cat-PAD), which is a combination of seven equimolar peptides targeting Fel d 1 [122]. This epitope vaccine effectively alleviated allergic symptoms in patients with cat allergies without causing any difference in acute allergic reactions, fluctuations in vital signs, or adverse events when compared to a placebo group in a clinical trial involving 14 allergic children [123].

6. Prospects of Prevention of Allergies

Allergens from pets remain a crucial factor in the induction of allergic rhinitis in humans. Currently, there are limited effective approaches to prevent allergies caused by cats and dogs, including allergen elimination or immune reaction inhibition. However, there is a lack of comprehensive research on integrating diverse preventive methods. During allergen production stages, pets can be fed with IgY antibodies targeting specifical allergens, while regular use of air purifiers can effectively eliminate residual airborne allergens. Furthermore, coordinated immunological interventions involving micronutrients supplementation with holoBLG can be implemented. By combining preventive measures that address distinct phases of the allergic response, it is possible to minimize allergy occurrence.

However, achieving complete eradication of environmental allergens remains unattainable, rendering individuals with cat allergies constantly susceptible and highlighting the imperfections in preventing human allergic reactions to cats and dogs. The IgY antibody treatment lacks comprehensive long-term clinical trial data, while additional allergens such as Cat-NPC2, Fel d S100, and Fel d Hp have been identified [129,130]. Current preventative strategies primarily target Fel d 1 and Can f 1, but fail to provide sufficient protection for the entire population. The primary challenge lies in facilitating precise allergen diagnosis for patients through accurate allergen screening methods, thereby offering personalized treatment strategies. Clinically, inhalant allergen screening methods predominantly consist of skin prick tests (SPT), intradermal tests, allergen nasal provocation tests, and serum IgE assays [131]. Notably, a report of 622 cat allergy sufferers revealed that 27.8% of patients tested positive exclusively on SPT, while only 2.6% tested positive solely on specific IgE assays. To overcome the occurrence of false negatives, multiple testing methods are recommended [132].

Once the specific allergen is identified, desensitization treatment can be combined with ASIT. This involves formulating a vaccine containing purified allergens and specific immunological adjuvants, which are administered in gradually increasing concentrations to induce immune tolerance towards the allergen in patients. Previous studies have demonstrated that the efficacy of

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ASIT is influenced by various factors. One challenge lies in the isolation and purification of allergens from natural extracts, which directly affects the subsequent purity and cost of allergen reagents [133]. Additionally, there is a concern regarding potential adverse reactions associated with natural allergen extracts [134].

Fortunately, advancements in proteomics, immunomics, and bioinformatics can effectively mitigate the adverse reactions, reduce costs, and expedite development timeframes of ASIT. Databases such as Uniprot (http://www.uniprot.org/) provide researchers with comprehensive annotations for over 60 million proteins [135]. while repositories like the RCSB Protein Data Bank (PDB) contain an extensive collection of over 210,000 3D structures [136]. When obtaining an antigen protein sequence through high-throughput sequencing, these databases can be effortlessly utilized to identify sequences exhibiting the highest conservation and homology to the target antigen. Furthermore, computational models such as SWISS-MODEL and AlphaFold2 accurately predict the 3D structures of unknown antigens. This enables a deeper understanding of their function and facilitates structural characterization of antigenic epitopes [137,138]. Numerous machine learning-based algorithms have been developed for predicting antigenic epitopes based on known protein structures. These tools facilitate the prediction and screening of various lymphocyte-binding epitopes, enabling the subsequent fusion of selected epitopes into a protein construct [139]. Tools like Expasy (https://www.expasy.org/) and AlphaFold2 can analyze secondary and tertiary structures, while servers such as ClusPro 2.0 (https://cluspro.org/login.php) and C-ImmSim (http://150.146.2.1/C-IMMSIM/index.php) allow for molecular docking simulations and immune simulations to assess the viability of the fusion epitope construct. Immunoinformatics-based vaccine design has demonstrated successful effects with other allergens (Table 4). Moten et al. used a series of immunoinformatics techniques to develop a vaccine targeting Amb a 11, a ragweed pollen protein. Serum tests conducted on patients allergic to ragweed revealed that the predicted MHC II epitopes were capable of stimulating T cells to generate IgG antibodies against ragweed pollen without being detected by IgE antibodies [161]. Finally, genetic engineering or chemical methods are employed to synthesize proteins, followed by the selection of appropriate adjuvants; molecular biology methods can be used to verify the immunogenicity of the fusion epitope protein *in vitro*.

7. Conclusions

Allergies induced by cats and dogs continue to pose a significant threat public health. Various allergens have been identified in these pets, and their pathogenic mechanisms have also been summarized. Currently, physical methods, gene editing techniques, and immunological strategies (such as ASIT, monoclonal antibodies and IgY) are being employed for the prevention of human allergies to cats and dogs. This review also discussed strategies for enhancing the effectiveness of immunotherapy and explores future prospects that can contribute to the prevention and control of human allergies to other allergens.

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Abbreviations

IgE	immunoglobulin E
WHO	World Health Organization
FcεRI	IgE receptor
LCN1	lipid transport protein 1
SCR1-SCR3	structurally conserved regions
DCs	dendritic cells

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HSPG	heparan sulfate proteoglycans
IgG	immunoglobulin G
IgA	immunoglobulin A
IgM	immunoglobulin M
IgD	immunoglobulin D
LPS	lipopolysaccharide
TLR	Toll-like receptor
TNF-α	tumor necrosis factor α
APCs	antigen-presenting cells
TCRs	T cell receptors
MHC	major histocompatibility complex
Th2	helper 2 cells
IL-4	interleukin 4
IL-5	interleukin 5
IL-13	interleukin 13
IL-9	interleukin 9
IL-10	interleukin 10
PECO	photoelectrochemical oxidative
PFD	Molekule filtration device
HFD	HEPA-assisted air filtration device
ASIT	allergen-specific immunotherapy
SCIT	subcutaneous immunotherapy
SLIT	sublingual immunotherapy
ILIT	intralymphatic immunotherapy
ELISA	enzyme-linked immunosorbent assay
IC50	half-maximal inhibitory concentration
IgY	immunoglobulin Y
BLG	β-lactoglobulin
AHR	aryl hydrocarbon receptor
CBP	carbohydrate-based particles
TSLP	thymic stromal lymphopoietin
EMV	eggplant mosaic virus
3D	three-dimensional
Cat-PAD	Cat Peptide Antigen Desensitization
SPT	skin prick tests
PDB	Protein Data Bank

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